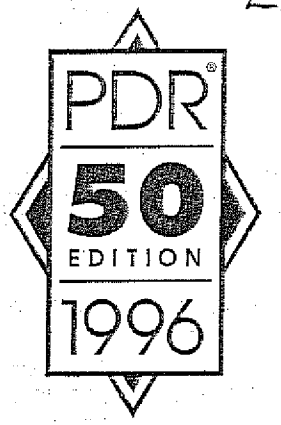
EXHIBIT A



PHYSICIANS' DESK REFERENCE®

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ISBNs: 1-56363-152-0 and 1-56363-156-3

experience with the penicillins
hown any positive evidence of
here are, however, no adequate
pregnant women showing con-
of these drugs on the fetus can
reproduction studies are not
response, this drug should be
if clearly needed.
s are excreted in human milk.
when penicillin G is adminis-

e excreted largely unchanged
mpletely developed renal func-
ination will be slow. Use cau-
orns and evaluate organ sys-

toxicity but does have a signif-
he following hypersensitivity
kin rashes ranging from mac-
tive dermatitis; urticaria; and
ckness, including chills, fever,
tion. Severe and occasionally
d (see "WARNINGS").
, thrombocytopenia, nephrop-
ly observed adverse reactions
th high intravenous dosage.
avenous therapy with penicil-
e (10 million to 100 million
even fatal potassium poison-
fficiency is present. Hyper-
a may be indicative of this

diac arrest may also occur.
ium may result in congestive
m intake.)
on has been reported in pa-

including convulsions, may
h CSF levels of beta-lactams.
ue medication, treat symp-
rtive measures as required.
dialyzable.

ATION
ible Strains of Streptococci,
—bacteremia, pneumonia,
ema, meningitis and other
f 5 million units daily.
may be used in the treat-
syphilis, but because of the
hospitalization is recom-
therapy will be determined
e disease.
imum of 5 million units

million units intramuscu-
s IV drip of 20–30 million

its/day for cervicofacial
r thoracic and abdominal

n units/day; penicillin is

infections of oropharynx,
nital area—5–10 million

Streptobacillus moniliformis
r 3–4 weeks.
ytogenes).
nits/day.
million units/day for 2

million units/day for 4

multocida).
million units/day for 2

a).
lay for 4–6 weeks.
E. coli, Enterobacter aer-
gella and *Proteus mirabi-*

lay.
400,000 units of penicil-
days.
units of penicillin/day in

ndocarditis[1] in patients
heumatic, or other ac-
ndergoing dental proce-
upper respiratory tract,
men. One million units
30,000 units/kg in chil-

Approx. Desired Concentration (units/ml)	Approx. Volume (ml) 1,000,000 units	Solvent for Vial of 5,000,000 units	Infusion Only 20,000,000 units
50,000	20.0	—	—
100,000	10.0	—	—
250,000	4.0	18.2	75.0
500,000	1.8	8.2	33.0
750,000	—	4.8	—
1,000,000	—	3.2	11.5

dren) intramuscularly mixed with 600,000 units procaine penicillin G (600,000 units for children) should be given one-half to one hour before the procedure. Oral penicillin V (phenoxymethyl penicillin), 500 mg for adults or 250 mg for children less than 60 lb, should be given every 6 hours for 8 doses. Doses for children should not exceed recommendations for adults for a single dose or for a 24 hour period.

Reconstitution

The following table shows the amount of solvent required for solution of various concentrations.

[See table above.]

When the required volume of solvent is greater than the capacity of the vial, the penicillin can be dissolved by first injecting only a portion of the solvent into the vial, then withdrawing the resultant solution and combining it with the remainder of the solvent in a larger sterile container.

Buffered Pfizerpen (penicillin G potassium) for Injection is highly water soluble. It may be dissolved in small amounts of Water for Injection, or Sterile Isotonic Sodium Chloride Solution for Parenteral Use. All solutions should be stored in a refrigerator. When refrigerated, penicillin solutions may be stored for seven days without significant loss of potency.

Buffered Pfizerpen for Injection may be given intramuscularly or by continuous intravenous drip for dosages of 500,000, 1,000,000, or 5,000,000 units. It is also suitable for intrapleural, intraarticular, and other local instillations.

THE 20,000,000 UNIT DOSAGE MAY BE ADMINISTERED BY INTRAVENOUS INFUSION ONLY.

(1) Intramuscular Injection: Keep total volume of injection small. The intramuscular route is the preferred route of administration. Solutions containing up to 100,000 units of penicillin per ml of diluent may be used with a minimum of discomfort. Greater concentration of penicillin G per ml is physically possible and may be employed where therapy demands. When large dosages are required, it may be advisable to administer aqueous solutions of penicillin by means of continuous intravenous drip.

(2) Continuous Intravenous Drip: Determine the volume of fluid and rate of its administration required by the patient in a 24-hour period in the usual manner for fluid therapy, and add the appropriate daily dosage of penicillin to this fluid. For example, if an adult patient requires 2 liters of fluid in 24 hours and a daily dosage of 10 million units of penicillin, add 5 million units to 1 liter and adjust the rate of flow so that the liter will be infused in 12 hours.

(3) Intrapleural or Other Local Infusion: If fluid is aspirated, give infusion in a volume equal to ¼ or ½ the amount of fluid aspirated, otherwise, prepare as for intramuscular injection.

(4) Intrathecal Use: The intrathecal use of penicillin in meningitis must be highly individualized. It should be employed only with full consideration of the possible irritating effects of penicillin when used by this route. The preferred route of therapy in bacterial meningitides is intravenous, supplemented by intramuscular injection.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Sterile solution may be left in refrigerator for one week without significant loss of potency.

HOW SUPPLIED

Buffered Pfizerpen (penicillin G potassium) for Injection is available in vials containing respectively 5,000,000 units × 10's (NDC 0049-0520-83), 5,000,000 units × 100's (NDC 0049-0520-95), 20,000,000 units × 1's (NDC 0049-0530-28), and a bulk pharmacy package of 20,000,000 units × 10's (NDC 0049-0530-83) of dry powder for reconstitution; buffered with sodium citrate and citric acid to an optimum pH.

Each million units contains approximately 6.8 milligrams of sodium (0.3 mEq) and 65.6 milligrams of potassium (1.68 mEq).

Store the dry powder below 86°F (30°C).

REFERENCE

1. American Heart Association. 1977. Prevention of bacterial endocarditis. Circulation. 56:139A–143A.

70-4209-00-5

SINEQUAN®

℞

[sin 'a-kwon]

(doxepin HCl)

Capsules

Oral Concentrate

DESCRIPTION

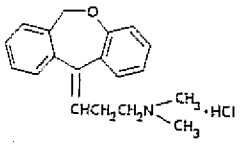
SINEQUAN® (doxepin hydrochloride) is one of a class of psychotherapeutic agents known as dibenzoxepin tricyclic compounds. The molecular formula of the compound is $C_{19}H_{21}NO \cdot HCl$ having a molecular weight of 316. It is a white crystalline solid readily soluble in water, lower alcohols and chloroform.

Inert ingredients for the capsule formulations are: hard gelatin capsules (which may contain Blue 1, Red 3, Red 40, Yellow 10, and other inert ingredients); magnesium stearate; sodium lauryl sulfate; starch.

Inert ingredients for the oral concentrate formulation are: glycerin; methylparaben; peppermint oil; propylparaben; water.

CHEMISTRY

SINEQUAN (doxepin HCl) is a dibenzoxepin derivative and is the first of a family of tricyclic psychotherapeutic agents. Specifically, it is an isomeric mixture of: 1-Propanamine, 3-dibenz [*b,e*] oxepin-11(6*H*)ylidene-*N,N*-dimethyl-, hydrochloride.



SINEQUAN (doxepin HCl)

ACTIONS

The mechanism of action of SINEQUAN (doxepin HCl) is not definitely known. It is not a central nervous system stimulant nor a monoamine oxidase inhibitor. The current hypothesis is that the clinical effects are due, at least in part, to influences on the adrenergic activity at the synapses so that deactivation of norepinephrine by reuptake into the nerve terminals is prevented. Animal studies suggest that doxepin HCl does not appreciably antagonize the antihypertensive action of guanethidine. In animal studies anticholinergic, antiserotonin and antihistamine effects on smooth muscle have been demonstrated. At higher than usual clinical doses, norepinephrine response was potentiated in animals. This effect was not demonstrated in humans.

At clinical dosages up to 150 mg per day, SINEQUAN can be given to man concomitantly with guanethidine and related compounds without blocking the antihypertensive effect. At dosages above 150 mg per day blocking of the antihypertensive effect of these compounds has been reported.

SINEQUAN is virtually devoid of euphoria as a side effect. Characteristic of this type of compound, SINEQUAN has not been demonstrated to produce the physical tolerance or psychological dependence associated with addictive compounds.

INDICATIONS

SINEQUAN is recommended for the treatment of:

1. Psychoneurotic patients with depression and/or anxiety.
2. Depression and/or anxiety associated with alcoholism (not to be taken concomitantly with alcohol).
3. Depression and/or anxiety associated with organic disease (the possibility of drug interaction should be considered if the patient is receiving other drugs concomitantly).
4. Psychotic depressive disorders with associated anxiety including involutional depression and manic-depressive disorders.

The target symptoms of psychoneurosis that respond particularly well to SINEQUAN include anxiety, tension, depression, somatic symptoms and concerns, sleep disturbances, guilt, lack of energy, fear, apprehension and worry.

Clinical experience has shown that SINEQUAN is safe and well tolerated even in the elderly patient. Owing to lack of clinical experience in the pediatric population, SINEQUAN is not recommended for use in children under 12 years of age.

Continued on next page

Roerig—Cont.

CONTRAINDICATIONS

SINEQUAN is contraindicated in individuals who have shown hypersensitivity to the drug. Possibility of cross sensitivity with other dibenzoxepines should be kept in mind.

SINEQUAN is contraindicated in patients with glaucoma or a tendency to urinary retention. These disorders should be ruled out, particularly in older patients.

WARNINGS

The once-a-day dosage regimen of SINEQUAN in patients with intercurrent illness or patients taking other medications should be carefully adjusted. This is especially important in patients receiving other medications with anticholinergic effects.

Usage in Geriatrics

The use of SINEQUAN on a once-a-day dosage regimen in geriatric patients should be adjusted carefully based on the patient's condition.

Usage in Pregnancy

Reproduction studies have been performed in rats, rabbits, monkeys and dogs and there was no evidence of harm to the animal fetus. The relevance to humans is not known. Since there is no experience in pregnant women who have received this drug, safety in pregnancy has not been established. There has been a report of apnea and drowsiness occurring in a nursing infant whose mother was taking SINEQUAN.

Usage in Children

The use of SINEQUAN in children under 12 years of age is not recommended because safe conditions for its use have not been established.

PRECAUTIONS

Drug Interactions:

Drugs Metabolized by P450 2D6: The biochemical activity of the drug metabolizing isozyme cytochrome P450 2D6 (debrisoquin hydroxylase) is reduced in a subset of the caucasian population (about 7–10% of caucasians are so-called "poor metabolizers"); reliable estimates of the prevalence of reduced P450 2D6 isozyme activity among Asian, African and other populations are not yet available. Poor metabolizers have higher than expected plasma concentrations of tricyclic antidepressants (TCAs) when given usual doses. Depending on the fraction of drug metabolized by P450 2D6, the increase in plasma concentration may be small, or quite large (8-fold increase in plasma AUC of the TCA).

In addition, certain drugs inhibit the activity of this isozyme and make normal metabolizers resemble poor metabolizers. An individual who is stable on a given dose of TCA may become abruptly toxic when given one of these inhibiting drugs as concomitant therapy. The drugs that inhibit cytochrome P450 2D6 include some that are not metabolized by the enzyme (quinidine; cimetidine) and many that are substrates for P450 2D6 (many other antidepressants, phenothiazines, and the Type 1C antiarrythmics propafenone and flecainide). While all the selective serotonin reuptake inhibitors (SSRIs), e.g., fluoxetine, sertraline, and paroxetine, inhibit P450 2D6, they may vary in the extent of inhibition. The extent to which SSRI-TCA interactions may pose clinical problems will depend on the degree of inhibition and the pharmacokinetics of the SSRI involved. Nevertheless, caution is indicated in the co-administration of TCAs with any of the SSRIs and also in switching from one class to the other. Of particular importance, sufficient time must elapse before initiating TCA treatment in a patient being withdrawn from fluoxetine, given the long half-life of the parent and active metabolite (at least 5 weeks may be necessary).

Concomitant use of tricyclic antidepressants with drugs that can inhibit cytochrome P450 2D6 may require lower doses than usually prescribed for either the tricyclic antidepressant or the other drug. Furthermore, whenever one of these drugs is withdrawn from co-therapy, an increased dose of tricyclic antidepressant may be required. It is desirable to monitor TCA plasma levels whenever a TCA is going to be coadministered with another drug known to be an inhibitor of P450 2D6.

MAO Inhibitors: Serious side effects and even death have been reported following the concomitant use of certain drugs with MAO inhibitors. Therefore, MAO inhibitors should be discontinued at least two weeks prior to the cautious initiation of therapy with SINEQUAN. The exact length of time may vary and is dependent upon the particular MAO inhibitor being used, the length of time it has been administered, and the dosage involved.

Cimetidine: Cimetidine has been reported to produce clinically significant fluctuations in steady-state serum concentrations of various tricyclic antidepressants. Serious anticholinergic symptoms (i.e., severe dry mouth, urinary retention and blurred vision) have been associated with elevations in the serum levels of tricyclic antidepressant when cimetidine therapy is initiated. Additionally, higher than expected tricyclic antidepressant levels have been observed when they are begun in patients already taking cimetidine. In patients who have been reported to be well controlled on tricyclic antidepressants receiving concurrent cimetidine therapy, discontinuation of cimetidine has been reported to decrease established steady-state serum tricyclic antidepressant levels and compromise their therapeutic effects.

Alcohol: It should be borne in mind that alcohol ingestion may increase the danger inherent in any intentional or unintentional SINEQUAN overdosage. This is especially important in patients who may use alcohol excessively.

Tolazamide: A case of severe hypoglycemia has been reported in a type II diabetic patient maintained on tolazamide (1 gm/day) 11 days after the addition of doxepin (75 mg/day).

Drowsiness

Since drowsiness may occur with the use of this drug, patients should be warned of the possibility and cautioned against driving a car or operating dangerous machinery while taking the drug. Patients should also be cautioned that their response to alcohol may be potentiated.

Suicide

Since suicide is an inherent risk in any depressed patient and may remain so until significant improvement has occurred, patients should be closely supervised during the early course of therapy. Prescriptions should be written for the smallest feasible amount.

Psychosis

Should increased symptoms of psychosis or shift to manic symptomatology occur, it may be necessary to reduce dosage or add a major tranquilizer to the dosage regimen.

ADVERSE REACTIONS

NOTE: Some of the adverse reactions noted below have not been specifically reported with SINEQUAN use. However, due to the close pharmacological similarities among the tricyclics, the reactions should be considered when prescribing SINEQUAN (doxepin HCl).

Anticholinergic Effects: Dry mouth, blurred vision, constipation, and urinary retention have been reported. If they do not subside with continued therapy, or become severe, it may be necessary to reduce the dosage.

Central Nervous System Effects: Drowsiness is the most commonly noticed side effect. This tends to disappear as therapy is continued. Other infrequently reported CNS side effects are confusion, disorientation, hallucinations, numbness, paresthesias, ataxia, extrapyramidal symptoms, seizures, tardive dyskinesia, and tremor.

Cardiovascular: Cardiovascular effects including hypotension, hypertension, and tachycardia have been reported occasionally.

Allergic: Skin rash, edema, photosensitization, and pruritus have occasionally occurred.

Hematologic: Eosinophilia has been reported in a few patients. There have been occasional reports of bone marrow depression manifesting as agranulocytosis, leukopenia, thrombocytopenia, and purpura.

Gastrointestinal: Nausea, vomiting, indigestion, taste disturbances, diarrhea, anorexia, and aphthous stomatitis have been reported. (See anticholinergic effects.)

Endocrine: Raised or lowered libido, testicular swelling, gynecomastia in males, enlargement of breasts and galactorrhea in the female, raising or lowering of blood sugar levels, and syndrome of inappropriate antidiuretic hormone secretion have been reported with tricyclic administration.

Other: Dizziness, tinnitus, weight gain, sweating, chills, fatigue, weakness, flushing, jaundice, alopecia, headache, exacerbation of asthma, and hyperpyrexia (in association with chlorpromazine) have been occasionally observed as adverse effects.

Withdrawal Symptoms: The possibility of development of withdrawal symptoms upon abrupt cessation of treatment after prolonged SINEQUAN administration should be borne in mind. These are not indicative of addiction and gradual withdrawal of medication should not cause these symptoms.

DOSAGE AND ADMINISTRATION

For most patients with illness of mild to moderate severity, a starting daily dose of 75 mg is recommended. Dosage may subsequently be increased or decreased at appropriate intervals and according to individual response. The usual optimum dose range is 75 mg/day to 150 mg/day.

In more severely ill patients higher doses may be required with subsequent gradual increase to 300 mg/day if necessary. Additional therapeutic effect is rarely to be obtained by exceeding a dose of 300 mg/day.

In patients with very mild symptomatology or emotional symptoms accompanying organic disease, lower doses may suffice. Some of these patients have been controlled on doses as low as 25-50 mg/day.

The total daily dosage of SINEQUAN may be given on a divided or once-a-day dosage schedule. If the once-a-day schedule is employed the maximum recommended dose is 150 mg/day. This dose may be given at bedtime. **The 150 mg capsule strength is intended for maintenance therapy only and is not recommended for initiation of treatment.**

Anti-anxiety effect is apparent before the antidepressant effect. Optimal antidepressant effect may not be evident for two to three weeks.

OVERDOSAGE

A. Signs and Symptoms

1. Mild: Drowsiness, stupor, dryness of mouth.
2. Severe: Respiratory depre convulsions, cardiac arrhyt

Also: urinary retention (blad trointestinal motility (paraly hypothermia), hypertension, reflexes.

B. Management and Treatment

1. Mild: Observation and sup usually necessary.
2. Severe: Medical manage overdosage consists of ag If the patient is conscious appriate precautions to prevent should be performed eve idly absorbed. The use of activ recommended, as has been co with saline for 24 hours or mo should be established in com sisted ventilation used if nece may be required for several apparent recovery has been should be treated with the a mic agent. It has been reporte ovascular and CNS symptom sant poisoning in adults may intravenous administration o stigmine salicylate. Because metabolized, the dosage sh quired. Convulsions may resp vulsant therapy; however, ate any respiratory depres diuresis generally are not of of overdosage due to high tis SINEQUAN.

HOW SUPPLIED

SINEQUAN® is available as capsul HCl equivalent to:

10 mg—100's (NDC 0662-5340-66), 1 82)

25 mg—100's (NDC 0662-5350-66), 1 82), 5000's (NDC 0662-5350-94)

50 mg—100's (NDC 0662-5360-66), 1 82), 5000's (NDC 0662-5360-94)

75 mg—100's (NDC 0662-5390-66), 1 82)

100 mg—100's (NDC 0662-5380-66), 1 82)

150 mg—50's (NDC 0662-5370-50), 5

SINEQUAN® Oral Concentrate is av tles (NDC 0662-5100-47) with an accom brated at 5 mg, 10 mg, 15 mg, 20 mg, contains doxepin HCl equivalent to prior to administration, SINEQUAN should be diluted with approximate whole or skimmed milk, or orange, gra or pineapple juice. SINEQUAN® Or physically compatible with a number ages. For those patients requiring who are on methadone maintenance Concentrate and methadone syrup with Gatorade®, lemonade, orange Tang®, or water; but not with grape storage of bulk dilutions is not recom 69-2135-00-8

Shown in Product Identification

SPECTROBID®

[spek 'trō-bid]

(bacampicillin HCl)

TABLETS

DESCRIPTION

SPECTROBID® (bacampicillin HCl) is picillin class of semi-synthetic penicil basic penicillin nucleus: 6-amin SPECTROBID, as well as ampicillin, analogues, is acid resistant and suitable tion.

SPECTROBID is the hydrochloride bonyloxyethyl ester of ampicillin and During the process of absorption from tract, SPECTROBID is hydrolyzed to well characterized and effective antibi 400 mg tablet of SPECTROBID is equ 280 mg of ampicillin.

Chemically, SPECTROBID is 1'-ethoxy (D-α aminophenylacetamido) -penicil

HOW SUPPLIED

DIPRIVAN Injection is available in ready to use 20 mL ampules, 50 mL infusion vials, and 100 mL infusion vials containing 10 mg/mL of propofol.
20 mL ampules (NDC 0310-0290-20)
50 mL infusion vials (NDC 0310-0290-50)
100 mL infusion vials (NDC 0310-0290-11)
Propofol undergoes oxidative degradation, in the presence of oxygen, and is therefore packaged under nitrogen to eliminate this degradation path.
Store below 22°C (72°F). Do not store below 4°C (40°F). Refrigeration is not recommended. Shake well before use.
Manufactured for:
ZENECA
Pharmaceuticals
A Business Unit of Zeneca Inc.
Wilmington, Delaware 19850-5437
PC 64071-00 Rev L 10/94

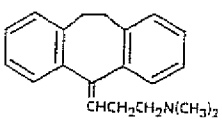
Shown in Product Identification Guide, page 341

ELAVIL®

amitriptyline HCl)
Tablets and Injection

DESCRIPTION

Amitriptyline HCl is 3-(10,11-dihydro-5*H*-dibenzo [*a,d*] cycloheptene-5-ylidene)-*N,N*-dimethyl-1-propanamine hydrochloride. Its empirical formula is $C_{20}H_{23}N \cdot HCl$ and its structural formula is:



Amitriptyline HCl, a dibenzocycloheptadiene derivative, has a molecular weight of 313.87. It is a white, odorless, crystalline compound which is freely soluble in water.
ELAVIL® (Amitriptyline HCl) is supplied as 10 mg, 25 mg, 50 mg, 75 mg, 100 mg, and 150 mg tablets and as a sterile solution for intramuscular use. Inactive ingredients of the tablets are calcium phosphate, cellulose, colloidal silicon dioxide, hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose, magnesium stearate, starch, stearic acid, talc, and titanium dioxide. Tablets ELAVIL 10 mg also contain FD&C Blue 1. Tablets ELAVIL 25 mg also contain D&C Yellow 10, FD&C Blue 1, and FD&C Yellow 6. Tablets ELAVIL 50 mg also contain D&C Yellow 10, FD&C Yellow 6 and iron oxide. Tablets ELAVIL 75 mg also contain FD&C Yellow 6. Tablets ELAVIL 100 mg also contain FD&C Blue 2 and FD&C Red 40. Tablets ELAVIL 150 mg also contain FD&C Blue 2 and FD&C Yellow 6. Each milliliter of the sterile solution contains:

Amitriptyline hydrochloride	10 mg
Glucose	44 mg
Water for Injection, q.s.	1 mL

Added as preservatives:

Methylparaben	1.5 mg
Propylparaben	0.2 mg

ACTIONS

ELAVIL is an antidepressant with sedative effects. Its mechanism of action in man is not known. It is not a monoamine oxidase inhibitor and it does not act primarily by stimulation of the central nervous system.
Amitriptyline inhibits the membrane pump mechanism responsible for uptake of norepinephrine and serotonin in adrenergic and serotonergic neurons. Pharmacologically this action may potentiate or prolong neuronal activity since uptake of these biogenic amines is important physiologically in terminating transmitting activity. This interference with the reuptake of norepinephrine and/or serotonin is believed by some to underlie the antidepressant activity of amitriptyline.

INDICATIONS

For relief of symptoms of depression. Endogenous depressions are more likely to be alleviated than are other depressive states.

CONTRAINDICATIONS

ELAVIL is contraindicated in patients who have shown hypersensitivity to it.
It should not be given concomitantly with monoamine oxidase inhibitors. Hyperpyretic crises, severe convulsions, and deaths have occurred in patients receiving tricyclic antidepressant and monoamine oxidase inhibiting drugs simultaneously. When it is desired to replace a monoamine oxidase inhibitor with ELAVIL, a minimum of 14 days should be allowed to elapse after the former is discontinued. ELAVIL should then be initiated cautiously with gradual increase in dosage until optimum response is achieved.
Use of drug is not recommended for use during the acute recovery phase following myocardial infarction.

WARNINGS

ELAVIL may block the antihypertensive action of guanethidine or similarly acting compounds.
It should be used with caution in patients with a history of seizures and, because of its atropine-like action, in patients with a history of urinary retention, angle-closure glaucoma or increased intraocular pressure. In patients with angle-closure glaucoma, even average doses may precipitate an attack.
Patients with cardiovascular disorders should be watched closely. Tricyclic antidepressant drugs, including ELAVIL, particularly when given in high doses, have been reported to produce arrhythmias, sinus tachycardia, and prolongation of the conduction time. Myocardial infarction and stroke have been reported with drugs of this class.
Close supervision is required when ELAVIL is given to hyperthyroid patients or those receiving thyroid medication. ELAVIL may enhance the response to alcohol and the effects of barbiturates and other CNS depressants. In patients who may use alcohol excessively, it should be borne in mind that the potentiation may increase the danger inherent in any suicide attempt or overdosage. Delirium has been reported with concurrent administration of amitriptyline and disulfiram.
Usage in Pregnancy: Teratogenic effects were not observed in mice, rats, or rabbits when amitriptyline was given orally at doses of 2 to 40 mg/kg/day (up to 13 times the maximum recommended human dose**). Studies in the literature have shown amitriptyline to be teratogenic in mice and hamsters when given by various routes of administration at doses of 28 to 100 mg/kg/day (9 to 33 times the maximum recommended human dose), producing multiple malformations. Another study in the rat reported that an oral dose of 25 mg/kg/day (8 times the maximum recommended human dose) produced delays in ossification of fetal vertebral bodies without other signs of embryotoxicity. In rabbits, an oral dose of 60 mg/kg/day (20 times the maximum recommended human dose) was reported to cause incomplete ossification of the cranial bones.
Amitriptyline has been shown to cross the placenta. Although a causal relationship has not been established, there have been a few reports of adverse events, including CNS effects, limb deformities, or developmental delay, in infants whose mothers had taken amitriptyline during pregnancy. There are no adequate or well-controlled studies in pregnant women. ELAVIL should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.
Nursing Mothers: Amitriptyline is excreted into breast milk. In one report in which a patient received amitriptyline 100 mg/day while nursing her infant, levels of 83–141 ng/mL were detected in the mother's serum. Levels of 135–151 ng/mL were found in the breast milk, but no trace of the drug could be detected in the infant's serum.
Because of the potential for serious adverse reactions in nursing infants from amitriptyline, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.
Usage in Children: In view of the lack of experience with the use of this drug in children, it is not recommended at the present time for patients under 12 years of age.

PRECAUTIONS

Schizophrenic patients may develop increased symptoms of psychosis; patients with paranoid symptomatology may have an exaggeration of such symptoms. Depressed patients, particularly those with known manic-depressive illness, may experience a shift to mania or hypomania. In these circumstances the dose of amitriptyline may be reduced or a major tranquilizer such as perphenazine may be administered concurrently.
The possibility of suicide in depressed patients remains until significant remission occurs. Potentially suicidal patients should not have access to large quantities of this drug. Prescriptions should be written for the smallest amount feasible.
Concurrent administration of ELAVIL and electroshock therapy may increase the hazards associated with such therapy. Such treatment should be limited to patients for whom it is essential.
When possible, the drug should be discontinued several days before elective surgery.
Both elevation and lowering of blood sugar levels have been reported.
ELAVIL should be used with caution in patients with impaired liver function.
Drug Interactions: Drugs Metabolized by P450 2D6—The biochemical activity of the drug metabolizing isozyme cytochrome P450 2D6 (debrisoquin hydroxylase) is reduced in a subset of the caucasian population (about 7-10% of caucasians are so called "poor metabolizers"); reliable estimates of the prevalence of reduced P450 2D6 isozyme activity among Asian, African and other populations are not yet available. Poor metabolizers have higher than expected plasma concentrations of tricyclic antidepressants (TCAs) when given usual doses. Depending on the fraction of drug metabolized by P450 2D6, the increase in plasma concentration may be small, or quite large (8-fold increase in plasma AUC of the TCA).
In addition, certain drugs inhibit the activity of this isozyme and make normal metabolizers resemble poor metabolizers. An individual who is stable on a given dose of TCA may become abruptly toxic when given one of these inhibiting drugs as concomitant therapy. The drugs that inhibit cytochrome P450 2D6 include some that are not metabolized by the enzyme (quinidine; cimetidine) and many that are substrates for P450 2D6 (many other antidepressants, phenothiazines, and the Type 1C antiarrhythmics propafenone and flecainide). While all the selective serotonin reuptake inhibitors (SSRIs), eg, fluoxetine, sertraline, and paroxetine, inhibit P450 2D6, they may vary in the extent of inhibition. The extent to which SSRI-TCA interactions may pose clinical problems will depend on the degree of inhibition and the pharmacokinetics of the SSRI involved. Nevertheless, caution is indicated in the coadministration of TCAs with any of the SSRIs and also in switching from one class to the other. Of particular importance, sufficient time must elapse before initiating TCA treatment in a patient being withdrawn from fluoxetine, given the long half-life of the parent and active metabolite (at least 5 weeks may be necessary).
Concomitant use of tricyclic antidepressants with drugs that can inhibit cytochrome P450 2D6 may require lower doses than usually prescribed for either the tricyclic antidepressant or the other drug. Furthermore, whenever one of these other drugs is withdrawn from co-therapy, an increased dose of tricyclic antidepressant may be required. It is desirable to monitor TCA plasma levels whenever a TCA is going to be coadministered with another drug known to be an inhibitor of P450 2D6.
Monoamine oxidase inhibitor—see CONTRAINDICATIONS section. Guanethidine or similarly acting compounds; thyroid medication; alcohol, barbiturates and other CNS depressants; and desulfiram—see WARNINGS section.
When ELAVIL is given with anticholinergic agents or sympathomimetic drugs, including epinephrine combined with local anesthetics, close supervision and careful adjustment of dosages are required.
Hyperpyrexia has been reported when ELAVIL is administered with anticholinergic agents or with neuroleptic drugs, particularly during hot weather.
Paralytic ileus may occur in patients taking tricyclic antidepressants in combination with anticholinergic-type drugs.
Cimetidine is reported to reduce hepatic metabolism of certain tricyclic antidepressants, thereby delaying elimination and increasing steady-state concentrations of these drugs. Clinically significant effects have been reported with the tricyclic antidepressants when used concomitantly with cimetidine. Increases in plasma levels of tricyclic antidepressants, and in the frequency and severity of side effects, particularly anticholinergic, have been reported when cimetidine was added to the drug regimen. Discontinuation of cimetidine in well-controlled patients receiving tricyclic antidepressants and cimetidine may decrease the plasma levels and efficacy of the antidepressants.
Caution is advised if patients received large doses of ethchlorvynol concurrently. Transient delirium has been reported in patients who were treated with one gram of ethchlorvynol and 75–150 mg of ELAVIL.
Information for Patients: While on therapy with ELAVIL, patients should be advised as to the possible impairment of mental and/or physical abilities required for performance of hazardous tasks, such as operating machinery or driving a motor vehicle.

ADVERSE REACTIONS

Within each category the following adverse reactions are listed in order of decreasing severity. Included in the listing are a few adverse reactions which have not been reported with this specific drug. However, pharmacological similarities among the tricyclic antidepressant drugs require that each of the reactions be considered when amitriptyline is administered.
Cardiovascular: Myocardial infarction; stroke; nonspecific ECG changes and changes in AV conduction; heart block; arrhythmias; hypotension, particularly orthostatic hypotension; syncope; hypertension; tachycardia; palpitation.
CNS and Neuromuscular: Coma; seizures; hallucinations; delusions; confusional states; disorientation; incoordination; ataxia; tremors; peripheral neuropathy; numbness, tingling, and paresthesias of the extremities; extrapyramidal symptoms including abnormal involuntary movements and tardive dyskinesia; dysarthria; disturbed concentration; excitement; anxiety; insomnia; restlessness; nightmares; drowsiness; dizziness; weakness; fatigue; headache; syndrome of inappropriate ADH (antidiuretic hormone) secretion; tinnitus; alteration in EEG patterns.
Anticholinergic: Paralytic ileus; hyperpyrexia; urinary retention, dilatation of the urinary tract; constipation;

Continued on next page

Zeneca Pharmaceuticals—Cont.

blurred vision, disturbance of accommodation, increased ocular pressure, mydriasis; dry mouth.
Allergic: Skin rash; urticaria; photosensitization; edema of face and tongue.
Hematologic: Bone marrow depression including agranulocytosis, leukopenia, thrombocytopenia; purpura; eosinophilia.
Gastrointestinal: Rarely hepatitis (including altered liver function and jaundice); nausea; epigastric distress; vomiting; anorexia; stomatitis; peculiar taste; diarrhea; parotid swelling; black tongue.
Endocrine: Testicular swelling and gynecomastia in the male; breast enlargement and galactorrhea in the female; increased or decreased libido; impotence; elevation and lowering of blood sugar levels.
Other: Alopecia; edema; weight gain or loss; urinary frequency; increased perspiration.
Withdrawal Symptoms: After prolonged administration, abrupt cessation of treatment may produce nausea, headache, and malaise. Gradual dosage reduction has been reported to produce, within two weeks, transient symptoms including irritability, restlessness, and dream and sleep disturbance.
These symptoms are not indicative of addiction. Rare instances have been reported of mania or hypomania occurring within 2–7 days following cessation of chronic therapy with tricyclic antidepressants.
Causal Relationship Unknown: Other reactions, reported under circumstances where a causal relationship could not be established, are listed to serve as alerting information to physicians:
Body as a Whole: Lupus-like syndrome (migratory arthritis, positive ANA and rheumatoid factor).
Digestive: Hepatic failure, ageusia.

DOSAGE AND ADMINISTRATION

Oral Dosage
Dosage should be initiated at a low level and increased gradually, noting carefully the clinical response and any evidence of intolerance.
Initial Dosage for Adults: For outpatients 75 mg of amitriptyline HCl a day in divided doses is usually satisfactory. If necessary, this may be increased to a total of 150 mg per day. Increases are made preferably in the late afternoon and/or bedtime doses. A sedative effect may be apparent before the antidepressant effect is noted, but an adequate therapeutic effect may take as long as 30 days to develop.
An alternate method of initiating therapy in outpatients is to begin with 50 to 100 mg amitriptyline HCl at bedtime. This may be increased by 25 or 50 mg as necessary in the bedtime dose to a total of 150 mg per day.
Hospitalized patients may require 100 mg a day initially. This can be increased gradually to 200 mg a day if necessary. A small number of hospitalized patients may need as much as 300 mg a day.
Adolescent and Elderly Patients: In general, lower dosages are recommended for these patients. Ten mg 3 times a day with 20 mg at bedtime may be satisfactory in adolescent and elderly patients who do not tolerate higher dosages.
Maintenance: The usual maintenance dosage of amitriptyline HCl is 50 to 100 mg per day. In some patients 40 mg per day is sufficient. For maintenance therapy the total daily dosage may be given in a single dose preferably at bedtime. When satisfactory improvement has been reached, dosage should be reduced to the lowest amount that will maintain relief of symptoms. It is appropriate to continue maintenance therapy 3 months or longer to lessen the possibility of relapse.
Intramuscular Dosage
Initially, 20 to 30 mg (2 to 3 mL) four times a day.
When ELAVIL Injection is administered intramuscularly, the effects may appear more rapidly than with oral administration.
When ELAVIL Injection is used for initial therapy in patients unable or unwilling to take ELAVIL Tablets, the tablets should replace the injection as soon as possible.
Usage in Children
In view of the lack of experience with the use of this drug in children, it is not recommended at the present time for patients under 12 years of age.
Plasma Levels
Because of the wide variation in the absorption and distribution of tricyclic antidepressants in body fluids, it is difficult to directly correlate plasma levels and therapeutic effect. However, determination of plasma levels may be useful in identifying patients who appear to have toxic effects and may have excessively high levels, or those in whom lack of absorption or noncompliance is suspected. Adjustments in dosage should be made according to the patient's clinical response and not on the basis of plasma levels.***

OVERDOSAGE

Manifestations: High doses may cause temporary confusion, disturbed concentration, or transient visual hallucinations. Overdosage may cause drowsiness; hypothermia; tachycardia and other arrhythmic abnormalities, such as bundle branch block; ECG evidence of impaired conduction; congestive heart failure; dilated pupils; disorders of ocular motility; convulsions; severe hypotension; stupor; coma; and, polyradiculoneuropathy. Other symptoms may be agitation, hyperactive reflexes, muscle rigidity, vomiting, hyperpyrexia, or any of those listed under ADVERSE REACTIONS.
There has been a report of fatal dysrhythmia occurring as late as 56 hours after amitriptyline overdose.
All patients suspected of having taken an overdosage should be admitted to a hospital as soon as possible. *Treatment* is symptomatic and supportive. Empty the stomach as quickly as possible by emesis followed by gastric lavage upon arrival at the hospital. Following gastric lavage, activated charcoal may be administered. Twenty to 30 g of activated charcoal may be given every four to six hours during the first 24 to 48 hours after ingestion. An ECG should be taken and close monitoring of cardiac function instituted if there is any sign of abnormality. Maintain an open airway and adequate fluid intake; regulate body temperature.
The intravenous administration of 1–3 mg of physostigmine salicylate is reported to reverse the symptoms of tricyclic antidepressant poisoning. Because physostigmine is rapidly metabolized, the dosage of physostigmine should be repeated as required particularly if life threatening signs such as arrhythmias, convulsions, and deep coma recur or persist after the initial dosage of physostigmine. Because physostigmine itself may be toxic, it is not recommended for routine use.
Standard measures should be used to manage circulatory shock and metabolic acidosis. Cardiac arrhythmias may be treated with neostigmine, pyridostigmine, or propranolol. Should cardiac failure occur, the use of digitalis should be considered. Close monitoring of cardiac function for not less than five days is advisable.
Anticonvulsants may be given to control convulsions. Amitriptyline increases the CNS depressant action but not the anticonvulsant action of barbiturates; therefore, an inhalation anesthetic, diazepam, or paraldehyde is recommended for control of convulsions.
Dialysis is of no value because of low plasma concentrations of the drug.
Since overdosage is often deliberate, patients may attempt suicide by other means during the recovery phase.
Deaths by deliberate or accidental overdosage have occurred with this class of drugs.

HOW SUPPLIED

Tablets ELAVIL, 10 mg, are blue, round, film coated tablets, identified with "40" debossed on one side and "ELAVIL" on the other side. They are supplied as follows:
NDC 0310-0040-10 bottles of 100
NDC 0310-0040-34 bottles of 1000
Tablets ELAVIL, 25 mg, are yellow, round, film coated tablets, identified with "45" debossed on one side and "ELAVIL" on the other side. They are supplied as follows:
NDC 0310-0045-10 bottles of 100
NDC 0310-0045-39 unit dose packages of 100
NDC 0310-0045-34 bottles of 1000
NDC 0310-0045-50 bottles of 5000
Tablets ELAVIL, 50 mg, are beige, round, film coated tablets, identified with "41" debossed on one side and "ELAVIL" on the other side. They are supplied as follows:
NDC 0310-0041-10 bottles of 100
NDC 0310-0041-39 unit dose packages of 100
NDC 0310-0041-34 bottles of 1000
Tablets ELAVIL, 75 mg, are orange, round, film coated tablets, identified with "42" debossed on one side and "ELAVIL" on the other side. They are supplied as follows:
NDC 0310-0042-10 bottles of 100
Tablets ELAVIL, 100 mg, are mauve, round, film coated tablets, identified with "43" debossed on one side and "ELAVIL" on the other side. They are supplied as follows:
NDC 0310-0043-10 bottles of 100
Tablets ELAVIL, 150 mg, are blue, capsule shaped, film coated tablets, identified with "47" debossed on one side and "ELAVIL" on the other side. They are supplied as follows:
NDC 0310-0047-30 bottles of 30
NDC 0310-0047-10 bottles of 100
Injection ELAVIL, 10 mg/mL, is a clear, colorless solution, and is supplied as follows:
NDC 0310-0049-10 in 10 mL vials
Storage: Store Tablets ELAVIL in a well-closed container. Avoid storage at temperatures above 30°C (86°F). In addition, Tablets ELAVIL 10 mg must be protected from light and stored in a well-closed, light-resistant container.
Protect ELAVIL Injection from freezing and avoid storage above 30°C (86°F).

METABOLISM

Studies in man following oral administration of ^{14}C-labeled drug indicated that amitriptyline is rapidly absorbed and metabolized. Radioactivity of the plasma was practically negligible, although significant amounts of radioactivity appeared in the urine by 4 to 6 hours and one-half to one-third of the drug was excreted within 24 hours.
Amitriptyline is metabolized by N-demethylation and bridge hydroxylation in man, rabbit, and rat. Virtually the entire dose is excreted as glucuronide or sulfate conjugate of metabolites, with little unchanged drug appearing in the urine. Other metabolic pathways may be involved.

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* Registered trademark of ZENECA Inc.
** Based on a maximum recommended amitriptyline dose of 150 mg/day or 3 mg/kg/day for a 50 kg patient.
*** Hollister LE: JAMA 1979;241:2550–2553.

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Shown in Product Identification Guide, page 342

HIBICLENS® Antiseptic/Antimicrobial Skin Cleanser (chlorhexidine gluconate)

OTC

[hi 'bi-klenz]

DESCRIPTION

HIBICLENS is an antiseptic antimicrobial skin cleanser possessing bactericidal activities. HIBICLENS contains 4% w/v HIBITANE® (chlorhexidine gluconate), a chemically unique hexamethylenebis biguanide with inactive ingredients: Fragrance, isopropyl alcohol 4%, purified water, Reg. 40, and other ingredients, in a mild, sudsing base adjusted to pH 5.0–6.5 for optimal activity and stability as well as compatibility with the normal pH of the skin.

ACTION

HIBICLENS is bactericidal on contact. It has antiseptic activity and a persistent antimicrobial effect with rapid bactericidal activity against a wide range of microorganisms, including gram-positive bacteria, and gram-negative bacteria such as *Pseudomonas aeruginosa*. The effectiveness of HIBICLENS is not significantly reduced by the presence of organic matter, such as blood.[1]
In a study[2] simulating surgical use, the immediate bactericidal effect of HIBICLENS after a single six-minute scrub resulted in a 99.9% reduction in resident bacterial flora with a reduction of 99.98% after the eleventh scrub. Reductions on surgically gloved hands were maintained over the six-hour test period.
HIBICLENS displays persistent antimicrobial action. In one study[2], 93% of a radiolabeled formulation of HIBICLENS remained present on uncovered skin after 6 hours.
HIBICLENS prevents skin infection thereby reducing the risk of cross-infection.

INDICATIONS

HIBICLENS is indicated for use as a surgical scrub, as a health-care personnel handwash, for patient preoperati